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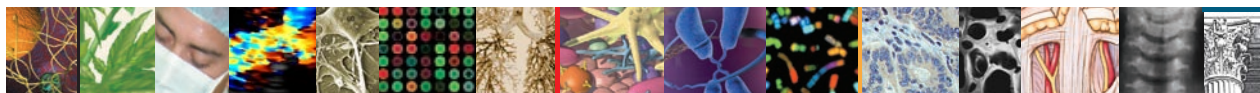
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An Uncertain Future for Cardiovascular Drug Development?

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The past year has been a challenging one for Pfizer, the world's largest pharmaceutical company. Its stock price has fallen as it has struggled to boost research productivity, going so far as to

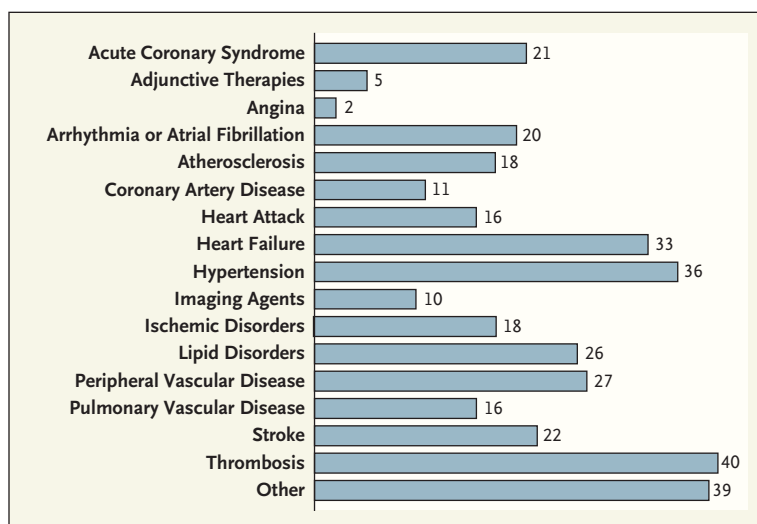
cut research jobs along with sales positions and spending \$68 billion to purchase Wyeth in a bid to strengthen its product portfolio. Its troubles are not recent, and when it announced last September that it was getting out of the business of developing new drugs to prevent or treat cardiovascular disease,¹ the news did not come as a complete surprise. The market for cardiovascular drugs was crowded, and Pfizer's recent efforts in the area had faltered: less than a year earlier, late clinical testing suggested that torcetrapib, a drug designed to increase levels of high-density lipoprotein cholesterol that had been Pfizer's greatest hope for replacing Lipitor

(atorvastatin) as a blockbuster product, increased mortality. Nevertheless, because Pfizer had prospered on the strong performance of its cardiovascular drugs — with nearly \$13 billion in sales in 2007, Lipitor was the world's top-selling drug — the announcement repudiated a strategy that had been spectacularly successful for years. Did the decision reflect only the strengths and weaknesses of Pfizer's pipeline, or have the commercial prospects soured so much that we can expect an industrywide decline in innovation in cardiovascular drugs?

Certainly the need for better ways to prevent and treat cardiovascular disease has not disap-

peared. Although age-adjusted death rates from heart and cerebrovascular disease continued to decline at least through 2005, heart disease remains the most common cause of death in the United States.² Aging of the populations of wealthy countries and the increasing prevalence of obesity and type 2 diabetes mellitus, along with rising incomes in much of the developing world, mean that the population at high risk for cardiovascular disease will expand worldwide in the coming years. Thus, despite the vagaries of the economy and gaps in health insurance coverage, the demand for cardiovascular drugs is not likely to collapse anytime soon.

Commercial success, however, depends on more than the number of patients who might benefit from treatment. With the growing acceptance of comparative effectiveness research, there are



Medicines in Development for Heart Disease and Stroke.

Some medicines are included in more than one category. Data are from PhRMA.⁴

strong pressures to compare new cardiovascular drugs to generic versions of effective drugs — such as high-potency statins — rather than to placebo. Generic statins have been on the market long enough to establish strong safety records and to produce myriad studies demonstrating that they prevent heart disease. Without proof of superior safety or effectiveness, an expensive new drug may not sell well. Furthermore, cholesterol reduction is only one of several potential strategies for preventing cardiovascular disease. Antihypertensive agents and aspirin confer additional protection. A “polypill” composed of low doses of well-tolerated, inexpensive drugs could reduce the relative risk of cardiovascular disease by as much as 80% and would be inexpensive and safe enough to be adopted with limited monitoring.³ Demonstrating that the addition of a new drug to any well-designed regimen for the prevention of heart disease improves health out-

comes — even if the regimen consists only of generic drugs — will be far more difficult than demonstrating superiority over placebo.

Safety standards are also likely to grow more stringent in the coming years. The Food and Drug Administration (FDA) takes a particularly hard look at drugs for conditions for which we already have safe and effective treatments, particularly if the incremental benefits appear to be small. The FDA is likely to scrutinize even more closely any drug for use by patients who can expect only small near-term benefits, such as young adults with few cardiac risk factors. If, instead, companies restrict testing to the populations most likely to benefit, such as people identified by genomic testing as appropriate candidates for treatment or patients with known coronary disease, they may need to limit marketing to narrowly targeted populations.

Pfizer announced that it was not cutting back its research in

other areas that it sees as more promising, such as Alzheimer’s disease and cancer. In the case of Alzheimer’s disease, a new drug would enter a market that offers few alternative treatments, none of which are fully satisfactory. And of the many treatments available for common cancers, none are curative and few have long-term efficacy. In either case, demand for an effective new product is likely to be less sensitive to price than is demand for drugs that prevent cardiovascular disease. Furthermore, safety standards are generally less rigorous for treatments for devastating conditions that have no effective treatment and for life-threatening illnesses. A redirection of drug-development activities is thus an appropriate response to anticipated changes in both the drug-approval process and the market for new drugs.

Pfizer’s decision was undoubtedly driven by an assessment of its drug pipeline and may not portend an industrywide shift away from cardiovascular drugs. Indeed, according to a recent report from the Pharmaceutical Research and Manufacturers of America (PhRMA), 312 medications for heart disease and stroke are currently under development (see graph).⁴ And Pfizer has already been shifting its focus to other areas; recent acquisitions and development partnerships had undoubtedly led the manufacturer to believe that its Alzheimer’s treatments were especially promising. Of course, such a strategy carries substantial risk. The inadequacy of existing treatments for Alzheimer’s disease is a sign of the difficulty of the scientific and clinical challenges. And

there are already many profitable markets within oncology, so success in this crowded area is far less likely to be driven by the dis-

innovation may be compounded by increasing regulatory burdens, as the FDA comes under intense pressure to raise preapproval safe-

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covery of an overlooked market than by a scientific breakthrough that leads to a substantially better product.

In these uncertain times, Pfizer's decision is a reminder that pharmaceutical innovation is vulnerable to market forces, changes in medical practice, and regulatory requirements. Efforts to bring health care costs under control and to rationalize health care delivery challenge the pharmaceutical industry. The greater price sensitivity of purchasers of drugs is both inevitable and necessary but means that the price premium for new drugs may be smaller than in the past. And drugs that produce only small incremental benefits over highly effective, low-cost alternatives are unlikely to command high prices or offer a favorable return on investment. If pharmaceutical firms are required to show that their new products are better than existing products rather than just placebo, they will need to conduct comparative trials that are much larger and more expensive than traditional phase 3 trials.

These shifts in the ways that pharmaceuticals are evaluated and purchased can ultimately improve the efficiency of health care. But their effects on pharmaceutical

ty standards. The pressure is a direct result of controversies over such widely used drugs as Avandia (rosiglitazone) and Vioxx (rofecoxib), which have led the press, government agencies, and Congress to question the transparency and completeness of safety reporting, as well as the effectiveness of the FDA's oversight.⁵ The perennial questions about balancing the risk that an unsafe product will be inappropriately approved for marketing against the possibility that an effective product will be delayed or never reach the market are, if anything, more relevant today than ever.

We need to know more about the safety and effectiveness of pharmaceutical products, yet simply demanding larger quantities of traditional preapproval safety information will raise the cost of bringing a drug to market, while doing little to prevent safety problems that become apparent only when large numbers of patients use the drug in routine clinical settings. The commitment, in the recently passed stimulus bill, to the wider adoption of health care information technology and to comparative effectiveness research means that it may soon be possible to do a much better job of monitoring phar-

maceutical safety and effectiveness after FDA approval. Ideally, this will make it possible to detect safety problems more reliably. A regulatory policy more closely aligned with improving postmarketing surveillance capabilities might not have deterred Pfizer from abandoning the development of new cardiovascular drugs, but it offers the best hope of ensuring that pharmaceutical innovation will continue without compromising safety.

Dr. Garber reports serving on the Medicare Coverage and Evidence Development Advisory Committee; serving on the board of directors of Exelixis; serving on advisory boards for the Blue Cross Blue Shield Association and Express Scripts; and receiving lecture fees from DeNovo Ventures, Express Scripts, and Covidien. No other potential conflict of interest relevant to this article was reported.

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